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White matter abnormalities in adults with 22q11 deletion syndrome with and without schizophrenia

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ABSTRACT

Dysfunction of cerebral white matter (WM) is a potential factor underlying the neurobiology of schizophrenia. People with 22q11 deletion syndrome have altered brain morphology and increased risk for schizophrenia, therefore decreased WM integrity may be related to schizophrenia in 22q11DS. We measured fractional anisotropy (FA) and WM volume in 27 adults with 22q11DS with schizophrenia (n = 12, 22q11DS SCZ+) and without schizophrenia (n = 15, 22q11DS SCZ−), 12 individuals with idiopathic schizophrenia and 31 age-matched healthy controls. We found widespread decreased WM volume in posterior and temporal brain areas and decreased FA in areas of the frontal cortex in the whole 22q11DS group compared to healthy controls. In 22q11DS SCZ+ compromised WM integrity included inferior frontal areas of parietal and occipital lobe. Idiopathic schizophrenia patients showed decreased FA in inferior frontal and insular regions compared to healthy controls. We found no WM alterations in 22q11DS SCZ+ vs. 22q11DS SCZ−. However, there was a negative correlation between FA and PANSS scores (Positive and Negative Symptom Scale) in the whole 22q11DS group in the inferior frontal, cingulate, insular and temporal areas. This is the first study to investigate WM integrity in adults with 22q11DS. Our results suggest that pervasive WM dysfunction is intrinsic to 22q11DS and that psychotic development in adults with 22q11DS involves similar brain areas as seen in schizophrenia in the general population.

1. Introduction

22q11 deletion syndrome (22q11DS) or velocardiofacial syndrome is caused by an interstitial deletion at the q11.2 locus of chromosome 22 (Carlson et al., 1997). This genetic disorder results in a variable clinical phenotype comprising somatic, cognitive, behavioral and psychiatric disorders, including schizophrenia-like psychosis (Murphy et al., 1999; Shprintzen, 2008). Therefore, the 22q11DS may provide valuable insight into the neuropathology associated with schizophrenia.

Brain imaging studies in 22q11DS have focused on identifying alterations in neural anatomy that might contribute to observed behavioral and psychiatric phenotypes associated with the syndrome. Several structural magnetic resonance imaging (MRI) studies have reported similarities in brain morphology in people with 22q11DS and in people with schizophrenia. These findings include enlarged corpus callosum and lateral ventricles and reduced total cerebral volume and gray matter volume of the fronto-temporal lobes (Shenton et al., 2001; Tan et al., 2009).

Over the last decade there has been growing evidence for the involvement of cerebral white matter (WM) in the psychopathology of schizophrenia (Walterfang et al., 2006; Konrad and Winterer, 2008; Connor et al., 2010). Volumetric MRI studies have found decreased WM volume in the corpus callosum, frontal and temporal lobes in schizophrenia (Kubicki et al., 2005; Williams, 2008). In 22q11DS reduced WM volume seems to occur early in life and in the absence of psychosis. Volumetric studies in children with 22q11DS report reduction of WM in frontal, parietal and temporal regions (Eliez et al., 2000, 2001; Kates et al., 2001; Simon et al., 2005; Campbell et al., 2006; Baker et al., 2011). However, a recent longitudinal study has shown increased WM volume in adolescents with 22q11DS (Kates et al., 2011). Moreover, a widespread loss of WM volume has been associated with the development of schizophrenia in adults with 22q11DS (van Amelsvoort et al., 2004).

Diffusion tensor imaging (DTI) is a neuroimaging technique employed for investigation of integrity of WM fibers beyond volumetric measurements. Brain WM consists of bundles of myelinated axons connecting several gray matter areas of the brain. Integrity of WM fibers

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is of vital importance for brain connectivity and information processing (Takeuchi et al., 2010). Therefore, disruption of WM integrity may account for some of the cognitive deficits and psychotic symptoms seen in schizophrenia and in 22q11DS.

DTI allows for quantification of diffusion of water molecules (expressed as fractional anisotropy (FA)) within axons (Basser, 1995). Lower FA is indicates lower connectivity or integrity of WM fibers (Beaulieu, 2002). DTI studies in schizophrenia reported reduced FA in frontal and temporal brain regions, in commissural and association WM fibers (Kanaan et al., 2005; Kubicki et al., 2007; Konrad et al., 2009; Peters et al., 2010). The few DTI studies that have been conducted in people with 22q11DS have been done in children and adolescents. These studies reported reduced FA in areas of the frontal, parietal and temporal lobes (Barnea-Goraly et al., 2003; Simon et al., 2005; Sundram et al., 2010) and clusters of increased FA from the posterior corpus callosum to the occipital lobes (Barnea-Goraly et al., 2003). Increased FA was also found in frontal and parietal clusters and in areas of the anterior to posterior cingulate gyrus, extending to the posterior corpus callosum and in the right inferior parietal lobe (Simon et al., 2005, 2008). Moreover, FA reductions in the left inferior parietal lobe correlated with poor arithmetic task performance (Barnea-Goraly et al., 2005). These findings suggest disturbed functional development of the brain in youth with 22q11DS. During transition to adulthood progressive and abnormal changes in brain structure in 22q11DS may take place that probably is critical for the development of schizophrenia. Furthermore, brain changes in 22q11DS patients with schizophrenia may develop in a distinctive manner compared to 22q11DS without schizophrenia with particular implication of WM (van Amelsvoort et al., 2004).

The aim of the study was to enhance our understanding of WM integrity in adults with 22q11DS and its association with symptoms of schizophrenia. Based on the above findings, we expected altered WM integrity in posterior and frontal brain areas in adults with 22q11DS. Moreover, we hypothesize that in 22q11DS with schizophrenia changes in FA would extend from parietal to fronto-temporal regions, perhaps showing similar FA aberrations as in idiopathic schizophrenia. In addition, we explored whether FA and WM volume differentiates between 22q11DS patients with and without schizophrenia.

2. Methods

2.1. Subjects

We included 27 adults with 22q11DS (mean ± SD) (22q11DS SCZ+ n = 12, age 31.17 ± 6.78; 22q11DS SCZ− n = 15, age 28.80 ± 8.56), 31 healthy controls (HC age 32.35 ± 9.74) and 12 males with idiopathic schizophrenia (age 23.33 ± 3.47).

Individuals with 22q11DS were recruited through the Dutch 22q11DS family association and several Dutch Clinical Genetics Centres. Individuals with idiopathic schizophrenia were recruited from the Adolescent Clinic of the Department of Psychiatry, Academic Medical Centre, University of Amsterdam (AMC). Healthy volunteers were recruited by local advertisement. The study was conducted at the Department of Psychiatry, Academic Medical Centre Amsterdam, The Netherlands and was approved by the local Medical Ethics Committee. All participants were capable of giving written informed consent and did so, after receiving full information on the study.

All individuals with 22q11DS were interviewed by a physician using semi-structured psychiatric interview. None of the healthy participants had a history of psychiatric disorders, medical conditions affecting brain function, substance or alcohol abuse and they were not using any medication at the time of testing. The 22q11DS group was subdivided into 2 groups: those who were fulfilling DSM-IV criteria for schizophrenia (22q11DS SCZ+) all taking antipsychotic medication and duration of illness >1 year) and those who did not have a psychiatric history (22q11DS SCZ−) and were neuroleptic and psychostimulant na ve. Clinical diagnoses of individuals with idiopathic schizophrenia were made according to the DSM-IV criteria by two psychiatrists independent of the study. Idiopathic schizophrenia patients were receiving care at the psychiatric open-ward inpatient and day care units of AMC, and were all medicated at the time of testing.

The Positive and Negative Symptom Scale (PANSS) (Kay et al., 1987) was used to assess positive, negative and general psychopathology in the patient groups. In addition, for assessment of intelligence quotient (IQ) we used the shortened Dutch version of the Wechsler Adult Intelligence Scale (WAIS-III NL) consisting of 5 subtests: vocabulary, comprehension, similarities (verbal IQ), block design, and object assembly (performance IQ) (Canavan et al., 1986; Wechsler, 1997).

2.2. MRI data acquisition

Whole brain magnetic resonance image (MRI) acquisition took place at the Department of Radiology (Academic Medical Centre Amsterdam, The Netherlands) using a 3 Tesla Intera MRI system (Philips, Best, The Netherlands) equipped with a 6 channel sense head coil.

DTI data were acquired using 3D multi-slice spin echo single shot echo-planar imaging with a repetition time (TR)/echo time (TE) 4834/94 diffusion sensitivities of $b = 0$ and $b = 1000$ s/mm^2; 32 diffusion gradient directions; 38 continuous (no inter-slice gap) slices, slice thickness 3 mm, 230 × 230 mm FOV; acquisition matrix 112 × 109; acquisition voxel size 2.05 × 2.10 × 3 mm.

For anatomical localization transversal high-resolution structural 3D T1-weighted sequences; full head coverage; TR/TE of 9.8/4.6 ms; axial orientation; 120 continuous (no inter-slice gap) slices; slice thickness 1.2 mm; flip angle 8°; 224 × 117 mm field of view (FOV); acquisition matrix 192 × 152 × 120; acquisition voxel size 1.17 × 1.17 × 1.20 mm.

2.3. MRI data processing

All data were processed using SPM8 (Statistical Parametric Mapping software, version 8, http://www.fil.ion.ucl.ac.uk/spm) and VBM8 (Voxel-Based Morphometry toolbox for SPM8) toolboxes on Matlab R2007a platform (The MathWorks Inc., USA version 7.4). To register the MRI images (T-1 weighed volumetric images and FA), we used the Diffeomorphic Anatomical Registration using Exponentiated Lie algebra algorithm (DARTEL) (Ashburner, 2007; Ashburner and Friston, 2009; Klein et al., 2009) tools integrated in both SPM8 and VBM8. Because DARTEL produces a more accurate registration, it improves the sensitivity of finding differences and localizing differences between groups in the concentration of WM. In order to normalize images to MNI space, an already existing DARTEL template in MNI space was used. This template was derived from 550 healthy European subjects of average age in IXI-database (http://www.brain-development.org). Therefore, no study-specific DARTEL template was created. All images were first converted from scanner-specific PAR/REC format to the NIFTI format.

T1-weighed images were checked for scanner artifacts and gross anatomical abnormalities. The individual T1 images were subsequently rigidly aligned to a pre-existing T1 template in MNI space. Following, individual probabilistic WM images were extracted using the VBM8 toolbox (http://dbm.neuro.uni-jena.de/vbm.html). Transformation parameters (flow-fields) and Jacobian determinants were calculated. The flow fields were applied to anatomically warp the individual WM probabilistic images to the DARTEL template and the Jacobian determinants were applied to modulate the warped images to account for local volume changes. The WM images were smoothed

with a Gaussian kernel of 12-mm full width at half-maximum (FWHM).

The DTI data were post processed using Philips Achieva software to create FA value maps. Image distortions in DTI data induced by eddy currents and head motion were corrected by applying a full affine alignment of each diffusion image to the mean no-diffusion-weighted image. The FA images were rigidly co-registered to the (segmented) WM image of the corresponding subject. As the FA closely resembles the WM images, and is in register with them, the flow fields that were used to warp WM to DARTEL space were also applied to the FA images in order to warp them directly into MNI space. Finally as with the VBM, the FA images were smoothed with a 12 mm FWHM Gaussian filter.

3. Statistical analysis

3.1. Demographic data

Group differences in age, IQ and PANSS were examined using analysis of variance (ANOVA). Group differences in gender were tested with Chi-square tests. Compiled data are expressed as mean ± SD. Level of statistical significance was defined as $P<0.05$ (two tailed). Statistical analyses were performed with SPSS, release 16.0.2 for Windows (SPSS Inc., Chicago, IL, USA).

3.2. Voxel-based analysis of fractional anisotropy and white matter volume

To test for FA and WM volume differences between 22q11DS patients, idiopathic schizophrenia and controls voxel-wise statistics were performed twice using independent-sample t-tests implemented in the general linear model approach of SPM8. In the first model without covariates, the analysis was conducted using t-contrasts "1 −1" for group A>B and "−1 1" for group A<B. Group comparisons were corrected for multiple comparisons using family wise error correction (FWE_{cor}) at cluster level $P<0.05$. In the second model, these same analyses for 22q11DS were performed including IQ as nuisance covariate, which means that all effects that can be explained by IQ were removed from the data. For the idiopathic schizophrenia group, analyses were performed including IQ, age and gender as covariate.

Voxel coordinates are given as an indication of location in a standardized brain. Additionally, resulting cluster maps of FA images were overlaid for visualization. Voxels and clusters were localized in Montreal Neurological Institute (MNI) space and transformed into Talairach and Tournoux coordinates. To further localize significant voxel clusters brain fibers up-to-date atlases were consulted (Talairach and Tournoux, 1988; Brett et al., 2002; Mori et al., 2005).

4. Results

4.1. Demographics

Demographics are displayed in Table 1. 22q11DS and healthy controls did not differ with regard to age (HC 32.35 ± 9.74, 22q11DS SCZ+ 31.17 ± 6.78, 22q11DS SCZ− 28.80 ± 8.56, $P=0.99$). The group of idiopathic schizophrenia patients was significantly younger than healthy controls (23.33 ± 3.47; $P=0.012$). Sex was significantly different between the groups; idiopathic schizophrenia group was composed exclusively of males (HC 17 m/14f, 22q11DS SCZ+ 7 m/5f, 22q11DS SCZ− 6 m/9f, idiopathic schizophrenia 12 m; $P=0.013$).

Patients had a lower total IQ than healthy controls (HC 104.13 ± 12.54, 22q11DS SCZ+ 67.50 ± 16.93, 22q11DS SCZ− 78.67 ± 7.57, idiopathic schizophrenia 88.50 ± 15.28; $P<0.001$). Total IQ was significantly different between HC vs. 22q11DS SCZ+ ($P<0.001$), HC vs. 22q11DS SCZ− ($P<0.001$) and HC vs. idiopathic schizophrenia ($P=0.027$). Total IQ was also significantly different between idiopathic schizophrenia vs. 22q11DS SCZ+ ($P=0.027$) and 22q11DS SCZ+ vs. 22q11DS SCZ− ($P=0.036$).

Table 1
Demographic and clinical variables (mean ± SD).

	22q11DS SCZ+	22q11DS SCZ−	Idiopathic SCZ	Healthy Controls
N (male/female)	7 m/5f	6 m/9f	12 m	17 m/14f
Age	31.17 ± 6.78	28.80 ± 8.56	23.33 ± 3.47	32.35 ± 9.74
IQ	67.50 ± 16.93	78.67 ± 7.56	88.50 ± 15.28	104.13 ± 12.53
PANSS positive scale	11.00 ± 3.55	7.46 ± 0.78	12.67 ± 2.93	
PANSS negative scale	17.64 ± 7.42	10.69 ± 2.63	13.33 ± 4.92	
PANSS general psychopathology scale	32.18 ± 10.39	22.15 ± 4.04	26.17 ± 5.42	
Total PANSS	60.82 ± 18.26	40.31 ± 5.76	52.17 ± 8.66	

PANSS: Positive and Negative Symptom Scale.

The mean scores on the PANSS subscales were significantly different between the patient groups ($P<0.05$). Scores on positive symptoms ($P=0.007$), negative symptoms ($P=0.008$) and general psychopathology ($P=0.004$) were significantly higher in 22q11DS SCZ+ vs. 22q11DS SCZ−. In addition, positive symptoms scores were significantly higher in idiopathic schizophrenia vs. 22q11DS SCZ− ($P=0.001$). The scores of total PANSS symptoms were higher in 22q11DS SCZ+ vs. 22q11DS SCZ− ($P=0.001$) and in idiopathic schizophrenia vs. 22q11DS SCZ− ($P=0.050$). There were no significant differences in the PANSS subscales between 22q11DS SCZ+ and idiopathic schizophrenia.

4.2. Fractional anisotropy

FA results including brain localization, voxel coordinates and P values for patient-controls and patient-patient comparisons are displayed in Table 2.

4.2.1. Patient–control and patient–patient comparisons — model without covariates

The whole 22q11DS group compared to healthy controls had significantly decreased FA in the right hemisphere in the pre-central and post-central areas ($FWE_{cor}=0.021$) and frontal sub-gyral ($FWE_{cor}=0.025$), and significantly increased FA in the anterior cingulate (bilaterally) ($FWE_{cor}=0.002$).

There was no decreased FA in 22q11DS SCZ+ patients compared to healthy controls surviving the correction for multiple comparisons but significantly increased FA in the left anterior cingulate and left frontal sub-gyral area ($FWE_{cor}=0.025$).

There was no decreased FA in 22q11DS SCZ− patients compared to healthy controls surviving the correction for multiple comparisons but significantly increased FA in the right frontal sub-gyral ($FWE_{cor}=0.006$).

There were no significant differences in FA in idiopathic SCZ patients compared to healthy controls surviving the correction for multiple comparisons. Also, there were no significant differences in FA in idiopathic SCZ patients compared to 22q11DS SCZ+ and in idiopathic SCZ compared to 22q11DS SCZ−.

4.2.2. Patient–control and patient–patient comparisons — model with covariates

The whole 22q11DS group compared to healthy controls had significantly decreased FA in the pre-central and post-central areas (bilaterally), in the right parietal sub-gyral ($FWE_{cor}<0.001$), right superior frontal area ($FWE_{cor}<0.001$) and in the parahippocampal area (bilaterally) ($FWE_{cor}=0.017$).

22q11DS SCZ+ patients compared to healthy controls had significantly decreased FA in several areas of the frontal lobes bilaterally,

Table 2
Fractional anisotropy: regions of significant differences between patients and healthy controls.

Cluster size	Brain area	*P* value	T & T			*Z* value	Tract
			x	*y*	*z*		
A. Model without covariates							
22q11DS Patients vs. HC							
Decreased FA							
1151	R frontal precentral	0.021	54	−3	31	4.30	slf
	R parietal postcentral		44	−19	42	4.23	slf
2778	R frontal sub-gyral	0.025	44	18	18	3.83	
Increased FA							
2155	L anterior cingulate	0.002	−9	38	9	4.39	cg/cc/gcc
	L frontal sub-gyral		15	41	6	3.86	cg/cc
	R anterior cingulate		−21	27	27	3.55	acr
22q11DS SCZ− vs. HC							
Increased FA							
3872	R frontal sub-gyral	0.006	26	26	19	3.53	cg/cc/acr
22q11DS SCZ+ vs. HC							
Increased FA							
2660	L anterior cingulate	0.025	−11	39	7	4.01	cg/cc
	L frontal sub-gyral		−20	24	28	3.69	cg/cc/acr
B. Model with covariates							
22q11DS Patients vs. HC							
Decreased FA							
5903	R superior frontal	0.001	21	8	56	4.14	cc/cg
2317	R frontal precentral	0.001	47	−4	43	3.83	slf
	R parietal sub-gyral		38	−31	43	3.62	slf
1679	L frontal precentral	0.005	−30	−13	54	3.84	slf
	L parietal postcentral		−45	−17	43	3.79	slf
1252	L parahippocampal	0.016	−28	−36	−5	3.20	ilf
1229	R parahippocampal	0.017	23	−19	−14	3.25	unc/ilf
22q11DS SCZ− vs. HC							
Decreased FA							
3196	L frontal precentral	0.000	−27	−10	56	4.11	slf
	L middle frontal		−26	3	57	4.15	slf/cc
3869	R frontal precentral	0.000	36	−18	55	4.58	slf
	R middle frontal		23	2	61	4.14	slf/cc
	R superior parietal		23	−61	56	4.13	slf
22q11DS SCZ+ vs. HC							
Decreased FA							
936	R frontal precentral	0.032	33	−9	49	4.16	slf
1841	L frontal precentral	0.003	−32	−16	54	4.01	slf
	L parietal postcentral		−41	−19	42	3.91	slf
4808	R parietal precuneus	0.001	27	−48	49	3.79	pcr
	R medial frontal		21	5	61	3.54	scr
5240	L inferior frontal	0.001	−35	26	−11	3.61	unc/ifo
	R inferior frontal		27	11	−18	3.41	unc/ifo
	R middle frontal		16	39	−20	3.37	ifo/cc/unc
7911	L middle occipital	0.001	−39	−78	16	4.00	ifo/ilf/ptr
Idiopathic SCZ vs. HC							
Decreased FA							
5637	R frontal sub-gyral	0.003	33	32	3	3.85	ifo/cc/unc
	R insula		44	5	12	3.76	slf
	R inferior frontal		44	27	−5	3.65	unc/ifo

$P_{FWE}<0.05$ corrected for multiple comparissons; L: left; R: right; T&T: Talairach and Tournoux coordinates of most significant voxels slf:superior longitudinal fascicuulus; cg: cingulum; cc: corpus callosum; acr: anterior corona radiata; unc: uncinate fasciculus; ifo: inferior fronto-occipital fasciculus; pcr: posterior corona radiata; scr: superior corona radiata; ilf: inferior longitudinal fasciculus; ptr: posterior thalamic radiation; scc: splenium of corpus callosum.

including inferior frontal area and in posterior areas of the brain including parietal and occipital regions ($FWE_{cor}<0.001$) (Fig. 1).

22q11DS SCZ− patients compared to healthy controls had significantly decreased FA in the precentral areas and the middle frontal areas (bilaterally) and in the right superior parietal sub-gyral area ($FWE_{cor}<0.001$). There was no significant increased FA in any of the above comparisons.

There was no significant decreased or increased FA in 22q11DS SCZ+ patients compared to 22q11DS SCZ− patients.

Idiopathic SCZ patients compared to healthy controls had significantly decreased FA in the right frontal sub-gyral area, right insula and right inferior frontal area ($FWE_{cor}<0.002$).

There were no significant differences in FA in idiopathic SCZ patients compared to 22q11DS SCZ+ and in idiopathic SCZ compared to 22q11DS SCZ−.

4.3. Correlation FA and PANSS in 22q11DS

In the whole 22q11DS group FA was negatively correlated with scores of the positive, negative and total symptoms of the PANSS scale. Table 3 shows the correlations between FA in the whole 22q11DS group and the PANSS including brain localization, voxel coordinates and *P* values.

Severity of positive symptoms was associated with significantly decreased FA in areas of the frontal (bilaterally) and right temporal areas ($FWE_{cor}<0.005$) (Fig. 2). Severity of negative symptoms associated with decreased FA in areas of the left frontal ($FWE_{cor}<0.001$) and left temporal lobe ($FWE_{cor}<0.005$). Scores of total PANSS including general psychopathology were associated with decreased FA in areas of the left temporal lobe and frontal lobe (bilaterally) ($FWE_{cor}<0.001$) and left insula ($FWE_{cor}=0.008$).

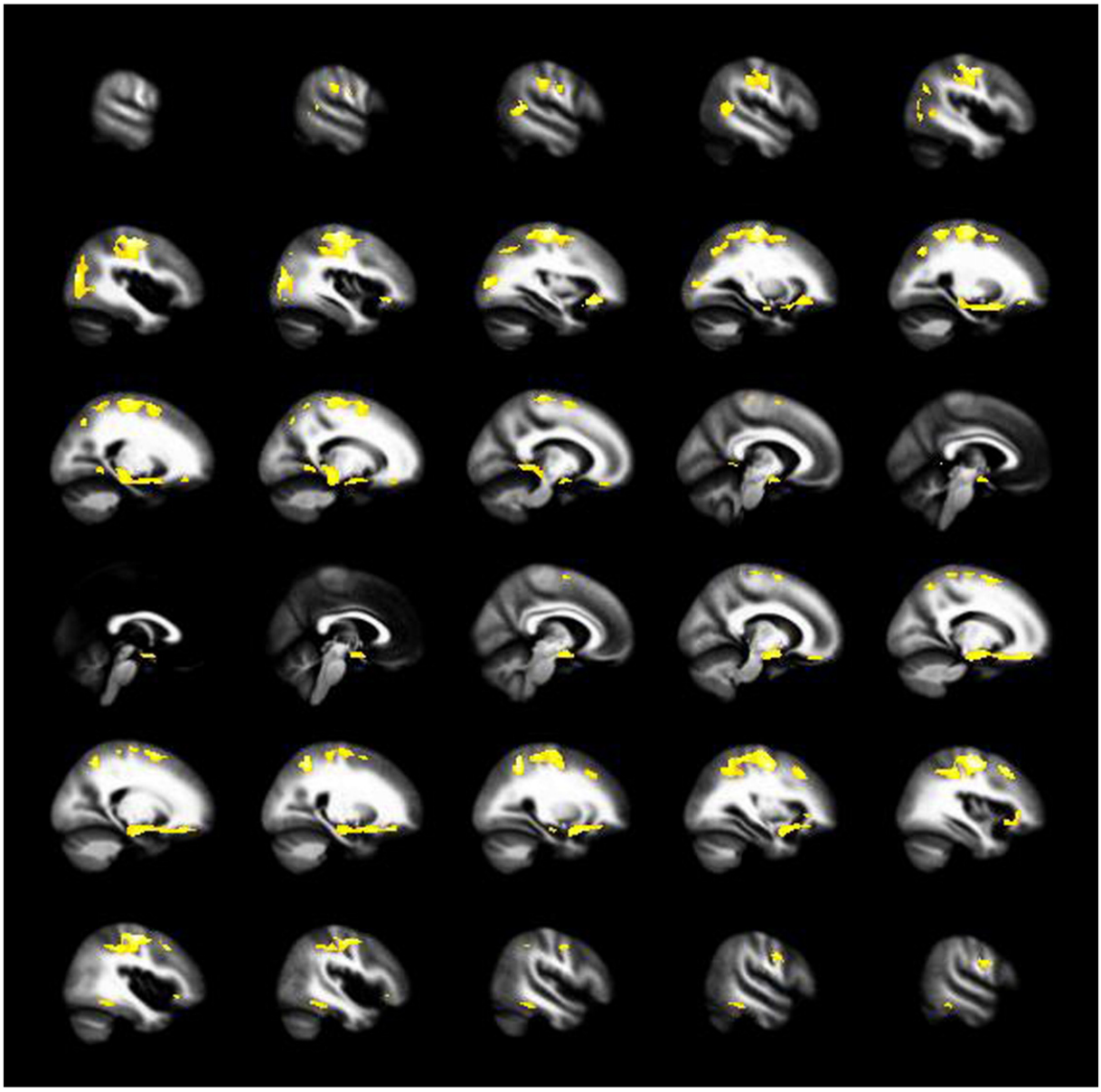

Fig. 1. Brain areas of decreased fractional anisotropy in 22q11DS patients with schizophrenia compared to healthy controls.

There was no significant correlation between PANSS scores and FA in idiopathic SCZ patients.

4.4. White matter volume

We found widespread WM decreases bilaterally in posterior areas in 22q11DS. WM results including brain localization, voxel coordinates and *P* values for patient–controls and patient–patient comparisons are displayed in Table 4.

4.4.1. Patient–control and patient–patient comparisons — model without covariates

The whole 22q11DS patients compared to healthy controls had significantly decreased WM volume in the occipital lobe (bilaterally), left middle frontal lobe and parahippocampal cortex and right pons ($FWE_{cor}<0.001$), left parietal subgyral and precuneus ($FWE_{cor}=0.007$).

22q11DS SCZ+ patients compared to healthy controls had significantly decreased WM volume in the occipital lobe (bilaterally), pons (bilaterally) and left temporal and parahippocampal lobe ($FWE_{cor}<0.001$).

22q11DS SCZ− patients compared to healthy controls had significantly decreased WM volume in the occipital lobe (bilaterally) and in the right pons ($FWE_{cor}<0.001$).

There was no significant decreased or increased WM volume in 22q11DS SCZ+ patients compared to 22q11DS SCZ− patients.

There were no significant differences in WM volume in idiopathic SCZ compared to healthy controls. Also, the comparisons of WM volume in idiopathic SCZ vs. 22q11DS SCZ+ and idiopathic SCZ vs. 22q11DS SCZ− showed no significant differences.

4.4.2. Patient–control and patient–patient comparisons — model with covariates

The whole 22q11DS patients compared to healthy controls had significantly decreased WM volume in the cuneus (bilaterally) ($FWE_{cor}<0.001$), right superior temporal lobe ($FWE_{cor}=0.001$) and in the post-central areas (bilaterally) ($FWE_{cor}=0.034$).

22q11DS SCZ+ patients compared to healthy controls had significantly decreased WM volume in the occipital lobe (bilaterally), right temporal sub-gyral ($FWE_{cor}<0.001$) and in the right pons ($FWE_{cor}<0.032$).

Table 3
Regions of significant negative correlation between FA and PANSS in the whole 22q11DS group.

Cluster size	Brain area	*P* value	T & T			*Z* value	Tract
			x	*y*	*z*		
Positive symptoms							
1632	R inferior frontal	0.002	30	18	−14	5.09	unc
	R superior temporal		35	6	−21	4.06	unc/ilf
	R inferior temporal		50	−5	−27	3.83	unc/ilf
1328	L inferior frontal	0.006	−24	26	−8	4.16	unc/ilf
	L frontal sub-gyral		−12	33	−14	3.83	unc/ifo/cc
	L frontal precentral		−33	−21	55	3.57	scr
Negative symptoms							
2456	L medial frontal gyrus	0.000	−8	−1	61	4.90	scr
	L frontal sub-gyral		−15	−22	43	4.59	scr
1224	L temporal sub-gyral	0.008	−47	−16	−20	4.00	ilf
	L pons		0	−31	−24	3.83	scp
Total psychopathology							
3890	L temporal sub-gyral	0.000	−50	−21	−18	4.81	ilf
1907	L medial frontal gyrus	0.001	−5	−1	59	4.52	scr
	L cingulate		−9	−4	43	4.35	cg
1220	L Sub-lobar Insula	0.008	35	19	5	4.40	unc/ifo
	R inferior frontal		30	22	−10	3.90	unc/ifo
	R frontal sub-gyral		12	16	−10	3.68	unc/ifo

$P_{FWE}<0.05$ corrected for multiple comparissons; L: left; R:right; T&T: Talairach and Tournoux coordinates of most significant voxels; unc:uncinate fasciculus; ilf:inferior longitudinal fasciculus; ifo:inferior fronto-occipital fasciculus; cc:corpus callosum; scr: superior corona radiata; scp:superior cerebellar penducle; cg:cingulum.

22q11DS SCZ− patients compared to healthy controls had significantly decreased WM volume in the occipital lobe (bilaterally) ($FWE_{cor}<0.001$), right superior temporal and parahippocampal areas ($FWE_{cor}=0.003$), right parietal post-central and precuneus ($FWE_{cor}=0.005$) and in the right pons ($FWE_{cor}=0.020$).

There was no significant decreased or increased WM volume in 22q11DS SCZ+ patients compared to 22q11DS SCZ− patients.

There were no significant differences in WM volume in idiopathic SCZ compared to healthy controls. There were no significant differences in WM volume in idiopathic schizophrenia compared to 22q11DS SCZ+ patients.

Idiopathic SCZ patients compared to 22q11DS SCZ− patients had significantly increased WM volume in the occipital cuneus (bilaterally) ($FWE_{cor}<0.001$).

5. Discussion

This is the first DTI study combined with VBM to investigate WM in adults with 22q11DS and its relation with schizophrenia. The results of this study show that reduced WM volume, particularly in posterior brain regions, is a typical feature of 22q11DS. Our findings confirmed the hypothesis of altered WM integrity posterior and frontal brain areas in adults with 22q11DS compared to healthy controls. Also, in line with our expectations we found decreased FA in posterior brain areas and widespread decreased FA in frontal lobes in 22q11DS SCZ+ compared to healthy controls. Particularly, findings in 22q11DS SCZ+ vs. controls resemble comparisons between idiopathic schizophrenia vs. controls, with FA reductions encompassing inferior frontal WM. Contrary to our expectations, we found no areas of increased or decreased FA and WM volume that could differentiate 22q11DS SCZ+ from 22q11DS SCZ−. In the whole 22q11DS group, scores of positive and negative symptoms were associated with reduced FA in areas previously implicated in schizophrenia mainly in frontal, cingulate, insula and temporal areas.

Earlier studies of brain volume in 22q11DS have proposed that WM alterations in 22q11DS affect particularly posterior areas of the brain (Eliez et al., 2000; Kates et al., 2001; Campbell et al., 2006). Similarly, we have found WM volumes decreased in occipital, parietal and temporal brain areas in the whole 22q11DS and in the patients subgroups (22q11DS SCZ+, 22q11DS SCZ−) compared to healthy controls. However, WM alterations in adults with 22q11DS are not limited to the posterior brain since our FA results showed decreased values in several brain regions including frontal lobes. The FA reductions that we observed in the whole 22q11DS sample are localized in WM areas encompassing fibers of the cingulum and corpus callosum, the superior longitudinal fasciculus, the inferior longitudinal and the uncinate fasciculus. These findings of decreased FA in 22q11DS are consistent with previous DTI studies investigating WM integrity in young people with 22q11DS (Barnea-Goraly et al., 2003; Simon et al., 2005; Sundram et al., 2010). Thus, alterations in fronto-parietal and fronto-temporal WM fibers may disrupt signal transmission and brain connectivity in adults with 22q11DS consequently implicating altered brain function and behavior.

Increased FA has been reported mainly in children and adolescents with 22q11DS in posterior areas of the brain (Barnea-Goraly et al., 2003; Simon et al., 2005, 2008). We found increased FA in the whole group of adults with 22q11DS in frontal and parietal areas encompassing WM fibers of the corpus callosum, cingulum, and from anterior to posterior corona radiate. However, in line with Sundram et al. (2010) the statistical significance of increased FA disappeared after covarying for IQ. The findings of increased FA, perhaps related to increased neuronal density or rearrangements of fiber organization, may be specific to the abnormal development of the brain in 22q11DS during childhood. Disproportional increases in WM volume and FA have also been reported in children with autism spectrum disorder (Ben et al., 2007; Cheng et al., 2010) and in young-onset schizophrenia (Douaud et al., 2009). However, increases in FA may be also due to the confounding effects of IQ. Earlier FA studies in children with 22q11DS did not control for cognitive disability (Barnea-Goraly et al., 2003; Simon et al., 2005, 2008), which is a well established feature of 22q11DS. Since we controlled for IQ, our findings of FA decreases instead of increases may be accurately attributed to 22q11DS. Moreover, a recent study showed reduction of total WM volume in adolescents with 22q11DS compared to IQ-matched controls suggesting that dysfunction of WM in 22q11DS is independent of IQ and inherent to 22q11DS (Baker et al., 2011).

For a better understanding of WM integrity in 22q11DS and its association with schizophrenia we split the 22q11DS group in 22q11DS SCZ+ and 22q11DS SCZ−. The comparison of the 22q11DS subgroups showed no differences in FA or WM volumes. Narrowing our comparison down to each 22q11DS subgroup vs. healthy individuals we observed similar areas of decreased WM volume in occipital lobes in both 22q11DS SCZ+ and 22q11DS SCZ−. But in 22q11DS SCZ− WM volume was also decreased in parietal brain regions. Moreover, in 22q11DS SCZ− compared to idiopathic schizophrenia we found lower WM volume areas of the occipital lobe. These findings indicate that disrupted WM in posterior brain is a typical feature of 22q11DS independent of schizophrenia. On the other hand, decreased FA in 22q11DS SCZ+ compared to healthy individuals affected mostly areas of frontal regions. Contrary to 22q11DS SCZ−, the 22q11DS SCZ+ had FA reductions in WM encompassing fibers of the inferior fronto-occipital, inferior longitudinal fasciculus and posterior thalamic radiation, the uncinate fasciculus and anterior corpus callosum compared to healthy controls. Furthermore, severity of symptoms of schizophrenia, including positive, negative and total psychopathology symptoms, in the whole 22q11DS group was associated with decreased FA in inferior frontal, cingulate, insula and temporal areas. Disruption of these WM networks is thought to contribute to psychotic symptoms and cognitive deficits in schizophrenia (Kubicki et al., 2007). Also, a meta-analysis of DTI studies in schizophrenia has identified FA reductions predominantly inferior frontal in WM fibers interconnecting the frontal lobe, thalamus and cingulate gyrus and in a network comprising the frontal lobe, insula, hippocampus–amygdala, temporal and occipital lobe (Ellison-Wright and Bullmore, 2009; Peters et al., 2010). In line with these findings, we

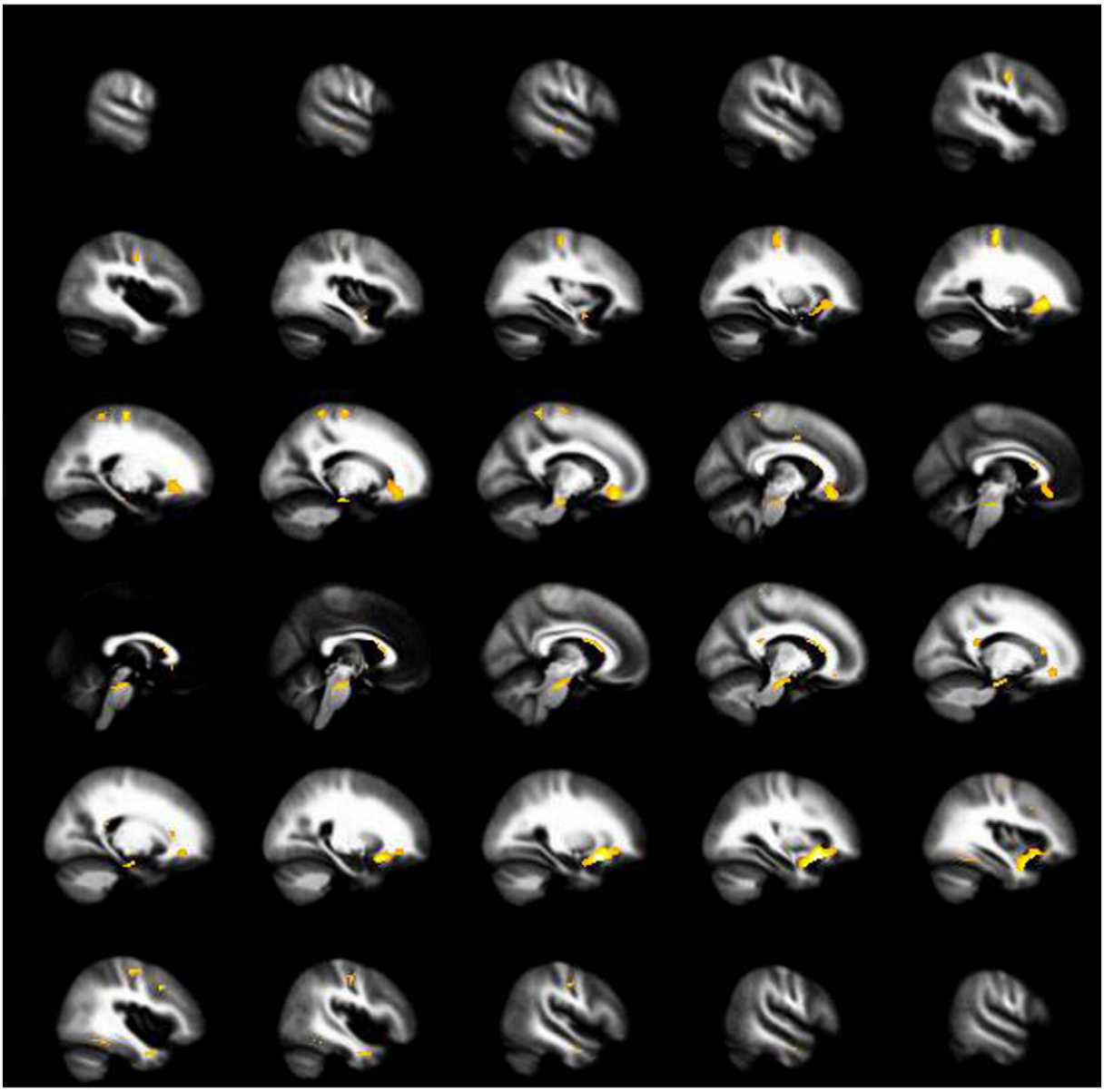

Fig. 2. Brain areas of negative correlation between positive symptoms and fractional anisotropy in 22q11DS patients.

report reduced FA in inferior frontal and in the insula encompassing WM fibers of the inferior fronto-occipital and the uncinate fasciculus in our group of idiopathic schizophrenia patients compared to healthy controls. Hence, our findings in 22q11DS may indicate the involvement of inferior frontal and temporal WM fibers in the development of schizophrenia in 22q11DS.

Several factors may contribute to disrupted WM integrity as measured by DTI. However, the cause and mechanism of dysfunction of WM anisotropy in people with 22q11DS is still subject to research. Altered anisotropy as measured by DTI may reflect abnormal coherence or organization of the fiber tracts, oligodendrocytes or myelin disruption. In schizophrenia, integrity of WM fibers has been associated with malfunction of genes and neurotransmitters (e.g. dopamine and glutamate) that are involved in oligodendrocyte and myelin development (Feng, 2008; Alix and Domingues, 2011). The same may hold for 22q11DS, particularly since people with 22q11DS are haploinsufficient for COMT and often also for PRODH (genes involved in dopaminergic and glutamatergic neurotransmission, respectively). Thus, haploinsufficiency of these, and perhaps other, genes in 22q11DS may be implicated in WM pathology associated with 22q11DS. For instance, we previously reported that genetic variation at the COMT and PRODH genes was associated with abnormal WM volume in schizophrenia (Zinkstok et al., 2008) and in 22q11DS (van Amelsvoort et al., 2008). In healthy children WM anisotropy was also altered depending on genetic variation at the COMT gene (Thomason et al., 2010). Further studies are needed to unravel the association between genetic variations in 22q11DS, neurotransmission and changes in anisotropy of WM.

Our study has several strengths. In contrast to earlier DTI studies in 22q11DS, this study included exclusively adults with 22q11DS allowing us to investigate WM integrity in the mature brain. In addition, to verify whether our findings in 22q11DS SCZ+ were related to schizophrenia we included a group of patients with idiopathic schizophrenia. We explored the relationship between WM changes and schizophrenia in 22q11DS presenting data uncorrected but also corrected for IQ, which provides insight in the relation between IQ and FA in 22q11DS. Furthermore the combined DTI and VBM measures allowed us to extend the findings of WM alterations in 22q11DS by differentiating areas of decreased WM volume from those of decreased FA.

Table 4
WM volume: regions of significant decreases between 22q11DS patients and healthy controls.

Cluster size	Brain area	*P* value	T & T			*Z* value
			x	*y*	*z*	
A. Model without covariates						
22q11DS Patients vs. HC						
26155	L occipital cuneus	0.000	−12	−76	9	7.24
	R occipital cuneus		17	−70	9	6.71
13265	R brainstem pons	0.000	5	−13	−26	6.04
5085	L parahippocampal	0.000	−27	−31	−3	5.13
	L middle frontal		−38	50	−12	4.6
2624	L parietal sub-gyral	0.007	−27	−42	51	4.1
	L parietal precuneus		−17	−54	55	3.76
22q11DS SCZ+ vs. HC						
5942	L occipital cuneus	0.000	−15	−76	9	5.64
	R occipital cuneus		2	−75	23	5.62
1351	R pons	0.000	3	−13	−24	4.74
	L pons		−8	−33	−21	4.51
951	L temporal sub-gyral	0.000	−29	−29	−3	5.1
	L parahippocampal		−15	−36	−2	4.51
22q11DS SCZ− vs. HC						
6114	L occipital cuneus	0.000	−12	−76	7	6.09
	R occipital cuneus		17	−72	9	5.42
729	R pons	0.001	3	−13	−26	4.92
B. Model with covariates						
22q11DS Patients vs. HC						
9329	L occipital cuneus	0.000	−11	−76	7	5.82
	R occipital cuneus		17	−70	9	5.06
2864	R brainstem pons	0.005	3	−13	−24	4.56
4405	R Superior Temporal lobe	0.001	50	−12	2	4.56
1568	L Parietal Postcentral lobe	0.034	−37	−19	45	4.66
3353	R Parietal Postcentral lobe	0.003	50	−12	40	4.11
22q11DS SCZ+ vs. HC						
3540	L occipital cuneus	0.002	−14	−75	6	4.24
	R occipital lingual		13	−89	2	3.91
3538	R temporal sub-gyral	0.002	35	−30	0	4.12
1557	R pons	0.032	2	−13	−23	3.69
22q11DS SCZ− vs. HC						
5853	L occipital cuneus	0.000	−12	−76	7	4.43
	R occipital cuneus		16	−69	13	4.12
3600	R superior temporal	0.003	47	0	−11	4.44
	R limbic parahippocampal		12	−36	−3	3.79
3233	R parietal postcentral	0.005	18	−40	63	4.14
	R parietal precuneus		18	−49	52	3.95
2146	R pons	0.020	2	−12	−24	4.14
22q11DS SCZ− vs. Idiopathic SCZ						
6645	R occipital cuneus	0.002	6	−85	25	5.04
	L occipital cuneus		−11	−73	12	4.76

$P_{FWE}<0.05$ corrected for multiple comparissons; L: left; R: right; T&T: Talairach and Tournoux coordinates of most significant voxels.

The results of the present study should be interpreted in light of the following considerations. First, the sample size, although quite large compared to previous studies, may have limited the power to detect WM alterations in 22q11DS SCZ+ vs. 22q11DS SCZ−. However, anatomical features including WM changes in 22q11DS SCZ+ and 22q11DS SCZ− may be of subtle and overlapping nature making discrimination between the groups difficult. The influence of medication cannot be ruled out; in schizophrenia antipsychotic treatments may modulate structural brain changes (Keshavan et al., 1998; Thompson et al., 2009). Also the sample size of patients with idiopathic schizophrenia may have been small to detect alterations in WM and significant correlation between FA and the PANSS scores. As brain changes in WM volume in schizophrenia may occur and progress differently across individuals over time (Olabi et al., 2011), the relatively early stage of the illness has possibly accounted for no changes in WM volume in our group of idiopathic schizophrenia compared to healthy controls. Lastly, voxel based analysis of FA does not provide information about specificity of brain fibers. Fiber-tracking and post-mortem methods are required to confirm the localization of affected WM fibers.

In summary, this study reports altered WM volume and FA in distinct areas of the brain in adults with 22q11DS. Our findings suggest that extensive decreased WM volume in posterior brain is intrinsic to 22q11DS and independent of the development of schizophrenia, whereas widespread decreased FA in frontal areas and consequently disrupted neuronal communication via WM fibers of the inferior frontal and temporal lobes may be related to psychotic symptoms in patients with 22q11DS SCZ+. Future multimodal imaging studies including fiber tracking and exploring genetic variations involved in WM integrity will help to clarify the role of WM in the vulnerability to schizophrenia in 22q11DS.

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Contributors

Fabiana da Silva Alves managed the literature searches, performed the experiments, analyses and wrote the manuscript.

Nicole Schmitz wrote the protocol and contributed with analysis of this manuscript.

Oswald Bloemen and Johan van der Meer analyzed the data for this manuscript.

Aart Nederveen, Julia Meijer, Erik Boot, Lieuwe de Haan, Don Linszen contributed materials, analysis tools and wrote the manuscript.

Therese van Amelsvoort designed the study, wrote the protocol and the manuscript.

All authors contributed to and have approved the final manuscript.

Conflict of interest

The authors declare that, except for income received from their primary employer, no other financial support or compensation has been received from any individual or corporate entity over the past 3 years for research or professional service.

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References

Alix, J.J., Domingues, A.M., 2011. White matter synapses: form, function, and dysfunction. Neurology 76, 397–404.
Ashburner, J., 2007. A fast diffeomorphic image registration algorithm. NeuroImage 38, 95–113.
Ashburner, J., Friston, K.J., 2009. Computing average shaped tissue probability templates. NeuroImage 45, 333–341.
Baker, K., Chaddock, C.A., Baldeweg, T., Skuse, D., 2011. Neuroanatomy in adolescents and young adults with 22q11 deletion syndrome: comparison to an IQ-matched group. NeuroImage 55, 491–499.
Barnea-Goraly, N., Menon, V., Krasnow, B., Ko, A., Reiss, A., Eliez, S., 2003. Investigation of white matter structure in velocardiofacial syndrome: a diffusion tensor imaging study. Am. J. Psychiatry 160, 1863–1869.
Barnea-Goraly, N., Eliez, S., Menon, V., Bammer, R., Reiss, A.L., 2005. Arithmetic ability and parietal alterations: a diffusion tensor imaging study in velocardiofacial syndrome. Brain Res. Cogn. Brain Res. 25, 735–740.
Basser, P.J., 1995. Inferring microstructural features and the physiological state of tissues from diffusion-weighted images. NMR Biomed. 8, 333–344.
Beaulieu, C., 2002. The basis of anisotropic water diffusion in the nervous system — a technical review. NMR Biomed. 15, 435–455.
Ben, B.D., Kronfeld-Duenias, V., Zachor, D.A., Ekstein, P.M., Hendler, T., Tarrasch, R., Even, A., Levy, Y., Ben, S.L., 2007. Accelerated maturation of white matter in young children with autism: a high b value DWI study. NeuroImage 37, 40–47.
Brett, M., Johnsrude, I.S., Owen, A.M., 2002. The problem of functional localization in the human brain. Nat. Rev. Neurosci. 3, 243–249.

Campbell, L.E., Daly, E., Toal, F., Stevens, A., Azuma, R., Catani, M., Ng, V., van, A.T., Chitnis, X., Cutter, W., Murphy, D.G., Murphy, K.C., 2006. Brain and behaviour in children with 22q11.2 deletion syndrome: a volumetric and voxel-based morphometry MRI study. Brain 129, 1218–1228.
Canavan, A.G.M., Dunn, G., McMillan, T.M., 1986. Principal components of the WAIS-R. Br. J. Clin. Psychology 25, 81–86.
Carlson, C., Sirotkin, H., Pandita, R., Goldberg, R., McKie, J., Wadey, R., Patanjali, S.R., Weissman, S.M., Anyane-Yeboa, K., Warburton, D., Scambler, P., Shprintzen, R., Kucherlapati, R., Morrow, B.E., 1997. Molecular definition of 22q11 deletions in 151 velo-cardio-facial syndrome patients. Am. J. Hum. Genet. 61, 620–629.
Cheng, Y., Chou, K.H., Chen, I.Y., Fan, Y.T., Decety, J., Lin, C.P., 2010. Atypical development of white matter microstructure in adolescents with autism spectrum disorders. NeuroImage 50, 873–882.
Connor, C.M., Crawford, B.C., Akbarian, S., 2010. White matter neuron alterations in schizophrenia and related disorders. Int. J. Dev. Neurosci. 29, 325–334.
Douaud, G., Mackay, C., Andersson, J., James, S., Quested, D., Ray, M.K., Connell, J., Roberts, N., Crow, T.J., Matthews, P.M., Smith, S., James, A., 2009. Schizophrenia delays and alters maturation of the brain in adolescence. Brain 132, 2437–2448.
Eliez, S., Schmitt, J.E., White, C.D., Reiss, A.L., 2000. Children and adolescents with velocardiofacial syndrome: a volumetric MRI study. Am. J. Psychiatry 157, 409–415.
Eliez, S., Blasey, C.M., Schmitt, E.J., White, C.D., Hu, D., Reiss, A.L., 2001. Velocardiofacial syndrome: are structural changes in the temporal and mesial temporal regions related to schizophrenia? Am. J. Psychiatry 158, 447–453.
Ellison-Wright, I., Bullmore, E., 2009. Meta-analysis of diffusion tensor imaging studies in schizophrenia. Schizophr. Res. 108, 3–10.
Feng, Y., 2008. Convergence and divergence in the etiology of myelin impairment in psychiatric disorders and drug addiction. Neurochem. Res. 33, 1940–1949.
Kanaan, R.A., Kim, J.S., Kaufmann, W.E., Pearlson, G.D., Barker, G.J., McGuire, P.K., 2005. Diffusion tensor imaging in schizophrenia. Biol. Psychiatry 58, 921–929.
Kates, W.R., Burnette, C.P., Jabs, E.W., Rutberg, J., Murphy, A.M., Grados, M., Geraghty, M., Kaufmann, W.E., Pearlson, G.D., 2001. Regional cortical white matter reductions in velocardiofacial syndrome: a volumetric MRI analysis. Biol. Psychiatry 49, 677–684.
Kates, W.R., Antshel, K.M., Faraone, S.V., Fremont, W.P., Higgins, A.M., Shprintzen, R.J., Botti, J.A., Kelchner, L., McCarthy, C., 2011. Neuroanatomic Predictors to prodromal psychosis in velocardiofacial syndrome (22q11.2 deletion syndrome): a longitudinal study. Biol. Psychiatry 69, 945–952.
Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr. Bull. 13, 261–276.
Keshavan, M.S., Schooler, N.R., Sweeney, J.A., Haas, G.L., Pettegrew, J.W., 1998. Research and treatment strategies in first-episode psychoses. The Pittsburgh experience. Br. J. Psychiatry 172, 60–65.
Klein, A., Andersson, J., Ardekani, B.A., Ashburner, J., Avants, B., Chiang, M.C., Christensen, G.E., Collins, D.L., Gee, J., Hellier, P., Song, J.H., Jenkinson, M., Lepage, C., Rueckert, D., Thompson, P., Vercauteren, T., Woods, R.P., Mann, J.J., Parsey, R.V., 2009. Evaluation of 14 nonlinear deformation algorithms applied to human brain MRI registration. NeuroImage 46, 786–802.
Konrad, A., Winterer, G., 2008. Disturbed structural connectivity in schizophrenia primary factor in pathology or epiphenomenon? Schizophr. Bull. 34, 72–92.
Konrad, A., Vucurevic, G., Musso, F., Stoeter, P., Dahmen, N., Winterer, G., 2009. ErbB4 genotype predicts left frontotemporal structural connectivity in human brain. Neuropsychopharmacology 34, 641–650.
Kubicki, M., McCarley, R.W., Shenton, M.E., 2005. Evidence for white matter abnormalities in schizophrenia. Curr. Opin. Psychiatry 18, 121–134.
Kubicki, M., McCarley, R., Westin, C.F., Park, H.J., Maier, S., Kikinis, R., Jolesz, F.A., Shenton, M.E., 2007. A review of diffusion tensor imaging studies in schizophrenia. J. Psychiatr. Res. 41, 15–30.
Mori, S., Wakana, S., Nagae-Poetscher, L., van Zijl, P., 2005. MRI Atlas of Human White Matter. Elsevier, Amsterdam.
Murphy, K.C., Jones, L.A., Owen, M.J., 1999. High rates of schizophrenia in adults with velo-cardio-facial syndrome. Arch. Gen. Psychiatry 56, 940–945.
Olabi, B., Ellison-Wright, I., McIntosh, A.M., Wood, S.J., Bullmore, E., Lawrie, S.M., 2011. Are there progressive brain changes in schizophrenia? A meta-analysis of structural magnetic resonance imaging studies. Biol Psychiatry. 70, 88–96.
Peters, B.D., Blaas, J., de, H.L., 2010. Diffusion tensor imaging in the early phase of schizophrenia: what have we learned? J. Psychiatr. Res. 44, 993–1004.
Shenton, M.E., Dickey, C.C., Frumin, M., McCarley, R.W., 2001. A review of MRI findings in schizophrenia. Schizophr. Res. 49, 1–52.
Shprintzen, R.J., 2008. Velo-cardio-facial syndrome: 30 years of study. Dev. Disabil. Res. Rev. 14, 3–10.
Simon, T.J., Ding, L., Bish, J.P., McDonald-McGinn, D.M., Zackai, E.H., Gee, J., 2005. Volumetric, connective, and morphologic changes in the brains of children with chromosome 22q11.2 deletion syndrome: an integrative study. NeuroImage 25, 169–180.
Simon, T.J., Wu, Z., Avants, B., Zhang, H., Gee, J.C., Stebbins, G.T., 2008. Atypical cortical connectivity and visuospatial cognitive impairments are related in children with chromosome 22q11.2 deletion syndrome. Behav. Brain Funct. 4, 25.
Sundram, F., Campbell, L.E., Azuma, R., Daly, E., Bloemen, O., Barker, G.J., Chitnis, X., Jones, D.K., van Amelsvoort, T., Murphy, K.C., Murphy, D.G.M., 2010. White matter microstructure in 22q11 deletion syndrome: a pilot diffusion tensor imaging and voxel-based morphometry study of children and adolescents. J. Neurodevelop. Disord. 2, 77–92.
Takeuchi, H., Sekiguchi, A., Taki, Y., Yokoyama, S., Yomogida, Y., Komuro, N., Yamanouchi, T., Suzuki, S., Kawashima, R., 2010. Training of working memory impacts structural connectivity. J. Neurosci. 30, 3297–3303.
Talairach, J., Tournoux, P., 1988. Co-planar stereotaxic atlas of the human brain Thieme, New York.
Tan, G.M., Arnone, D., McIntosh, A.M., Ebmeier, K.P., 2009. Meta-analysis of magnetic resonance imaging studies in chromosome 22q11.2 deletion syndrome (velocardiofacial syndrome). Schizophr. Res. 115, 173–181.
Thomason, M.E., Dougherty, R.F., Colich, N.L., Perry, L.M., Rykhlevskaia, E.I., Louro, H.M., Hallmayer, J.F., Waugh, C.E., Bammer, R., Glover, G.H., Gotlib, I.H., 2010. COMT genotype affects prefrontal white matter pathways in children and adolescents. Neuroimage 53, 926–934.
Thompson, P.M., Bartzokis, G., Hayashi, K.M., Klunder, A.D., Lu, P.H., Edwards, N., Hong, M.S., Yu, M., Geaga, J.A., Toga, A.W., Charles, C., Perkins, D.O., McEvoy, J., Hamer, R.M., Tohen, M., Tollefson, G.D., Lieberman, J.A., 2009. Time-lapse mapping of cortical changes in schizophrenia with different treatments. Cereb. Cortex 19, 1107–1123.
Van Amelsvoort, T., Daly, E., Henry, J., Robertson, D., Ng, V., Owen, M., Murphy, K.C., Murphy, D.G., 2004. Brain anatomy in adults with velocardiofacial syndrome with and without schizophrenia: preliminary results of a structural magnetic resonance imaging study. Arch. Gen. Psychiatry 61, 1085–1096.
Van Amelsvoort, T., Zinkstok, J., Figee, M., Daly, E., Morris, R., Owen, M.J., Murphy, K.C., de, H.L., Linszen, D.H., Glaser, B., Murphy, D.G., 2008. Effects of a functional COMT polymorphism on brain anatomy and cognitive function in adults with velo-cardio-facial syndrome. Psychol. Med. 38, 89–100.
Walterfang, M., Wood, S.J., Velakoulis, D., Pantelis, C., 2006. Neuropathological, neurogenetic and neuroimaging evidence for white matter pathology in schizophrenia. Neurosci. Biobehav. Rev. 30, 918–948.
Wechsler, D., 1997. WAIS-III: Wechsler Adult Intelligence Scale. Administration and Scoring Manual3rd ed. edn. TX: Psychological Corporation, San Antonio.
Williams, L.M., 2008. Voxel-based morphometry in schizophrenia: implications for neurodevelopmental connectivity models, cognition and affect. Expert. Rev. Neurother. 8, 1049–1065.
Zinkstok, J., Schmitz, N., van, A.T., Moeton, M., Baas, F., Linszen, D., 2008. Genetic variation in COMT and PRODH is associated with brain anatomy in patients with schizophrenia. Genes Brain Behav. 7, 61–69.